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Review Article

Probiotics: An Adjuvant therapy for D-Galactose induced Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a chronic and slowly progressing neurodegenerative disorder which has become a major health concern worldwide. The literature has shown that oxidative stress is one of the most important risk factors behind the cause of AD. Oxidative stress often leads to the production of Reactive Oxygen Species (ROS).

D-Galactose, a physiological nutrient and reducing sugar, non-enzymatically reacts with amines of amino acids in proteins and peptides to form Advanced Glycation End products which activate its receptors coupled to Biochemical pathways that stimulate free radical production and induces mitochondrial dysfunction which damages the neuron intracellularly. High dosage of D-Galactose also suppresses the expression of nerve growth factors and its associated protein which results in the degeneration of nerve cells and reduction of acetylcholine levels in brain regions.

This article put forwards the advantages of using Lactic Acid Bacteria (Probiotics) possessing anti-oxidant properties and which produces Acetyl Choline against D-Galactose induced Alzheimer's disease.

Keywords: D-Galactose, Alzheimer's disease, Adjuvant therapy, Probiotics.

Introduction

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorder in the aged people across the world. Till date worldwide, nearly 44 million people have been affected by Alzheimer's related dementia and it is estimated that more than 4 million and 5.3 million individuals have Alzheimer's disease in India and the United States, respectively [1,2].

It is projected that more than 13.5 million individuals will be having AD by the year 2050 [3]. AD is clinically characterized on the basis of the brain pathological hallmarks such as dystrophic neuritis, neurofibrillary tangles and β amyloid plaques derived from the amyloid precursor proteins [4].

Neurotoxicity of amyloid plaques not only increases oxidative stress which causes low-grade inflammation by activating the nuclear factor-kappa B (NF-κB) signalling pathway but also, accelerates the aging process which further leads to the generation of reactive oxygen species (ROS) [5-7]. ROS is involved in mitochondrial dysfunction and damage of neuronal membranes, proteins, lipids, and nucleic acids [8].

Prolonged supplementation of D-Galactose induces oxidative stress followed by mitochondrial dysfunction and intracellular damage of neurons, accelerating aging, and influencing age-related cognitive decline in experimental animals [9].

D-Galactose Induced Alzheimer's Disease

D-Galactose induces aging-inducible oxidative stress in vivo, which resembles the natural aging process in mice [10, 11]. D-Galactose is metabolized to galactose-1-phosphate at a normal concentration by D-galactokinase or galactose-1-phosphate uridyl-transferase, but not at high levels. Instead, at increased concentration, D-galactose is converted to galactitol, which accumulates in cells and then induces osmotic stress and generates reactive oxygen species (ROS) which induces mitochondrial dysfunction and is the major cause of intracellular damage [12]. D-Galactose also reacts with the free amines of amino acids in peptides and proteins forming advanced glycation end-products (AGE) [13]. High dosage of D-Galactose also suppresses the expression of nerve growth factors and its associate protein resulting in the degeneration of nerve cells and reduction of acetylcholine levels in brain regions (Figure 1).

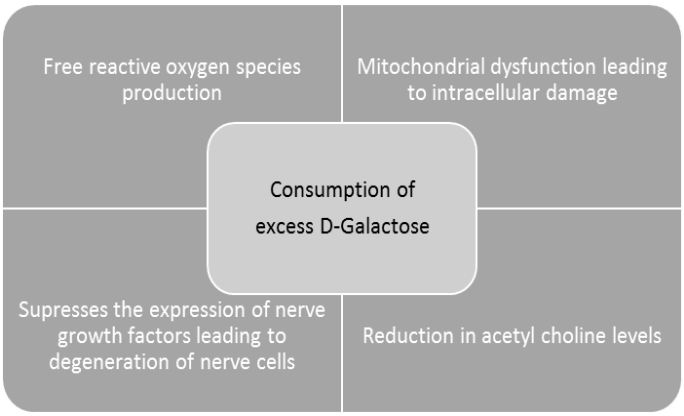

Figure 1. D-Galactose induced Alzheimer's Disease

ROS activate inflammatory signaling molecules, such as the phosphatidylinositol 3-kinase (PI3K), nuclear factor-kappa B (NF-kB), Janus kinase (JAK) and mitogen-activated protein kinases (MAPK). It also induces the expression of tumor necrosis factor-alpha, interleukin-1b (IL-1b) and IL-6 [14]. D-Galactose increases replicative senescence markers p16 expression and telomere shortening but reduces doublecortin (DCX) expression [15]. Therefore, D-galactose continuously

stimulates low-grade inflammation, which is associated with the acceleration of aging.

Lactic Acid Bacteria (Probiotics) and D-Galactose Induced Alzheimer's Disease

Lactic acid bacteria (LAB) are gram-positive, acid-tolerant and generally non-sporulating bacteria. The LAB is found in various food stuff like cheese, yogurt, and among the vagina and gastrointestinal microbiota. Most of LAB, Lactobacilli and Bifidobacteria, are microorganisms deemed beneficiall to us since they produce lactic acid as a major end product. Therefore, they are considered as safe products, due to their ubiquitous appearance in food and their contribution to the healthy microbiota [16].

Lactobacillus is a gram-positive facultative anaerobic or microaerophilic rod-shaped bacteria. They also possesss various properties like anticancer, antioxidant, antidiabetic, antiobesity, and antihyperlipidemic effects [17].

Recent studies have found that the L. plantarum versus pentosus showed a protective effect against memory deficit in AD-induced mice by D-Galactose and scopolamine [13,18]. Further, another study reported that L. Plantarum NDC75017 improves the learning and memory ability in aging rats [19]. Previous reports proved that strong antioxidants increases the Na+, K+-ATPases activities by decreasing AChE (Acetyl cholinesterase) levels and improves the cognition by enhancing cholinergic transmission [20].

Lactobacillus plantarum MTCC1325 strain has the ability to produce Acetylcholine Neurotransmitter via both externally and internally pathway [21] and this strain also possess potential antioxidant activity.

Chronic injection of D-Galactose induces memory impairment, neurodegeneration and oxidative damage in mice [22]. L. plantarum MTCC 1325 has the ability to produce the neurotransmitter viz. Acetylcholine [23] and also possesses potential antioxidant activity.

Biochemically, it was well established that AD has been related to a significant decrease in the brain neurotransmitter ACh [24] and oxidative stress, eventually leading to imbalance production and detoxification of ROS, which is considered to be the important factor in the development of AD. AD-model rats showed a significant decline in total body weight, organ index, hair loss and skin elasticity[25]. Chronic administration of D-Galactose caused significant decline in spatial memory and reduced gross behaviorall activity which suggests impairment of memory [9].

From the comparative studies conducted for 60 days in rats, it was evident that chronic administration of L. plantarum MTCC1325 for 60 days showed significant improvement and recovery from AD. There was significant improvement in the activities of the membrane transport ATPases system in the selected brain regions of AD-induced group as well. Further, it was revealed that L. Plantarum MTCC1325 protects the neurons by stabilizing the structural and functional integrity of the biological membranes through the regulation of ionic concentration gradient by its antioxidant properties [26].

Similarly, the results on the cholinergic system indicated that chronic administration of D-Galactose caused a significant reduction in ACh level in brain due to dysfunction of cholinergic neurons and reduced activity of Choline acetyltransferase [27] while elevation in AChE activity was responsible for cognitive deficit, this condition was significantly ameliorated in both the regions of brain such as hippocampus and cerebral cortex by oral supplementation of L. plantarum MTCC1325.

This may be associated with its potential antioxidant nature, Acetylcholine producing activities of L. plantarum MTCC1325 and also bidirectional communication between the Gut-Bain Axis (Enteric Nervous System) [28]. The recent reviews on Gut-Bain Axis communication describe the bacteria (micro biome) present in the gastro-intestinal tract may communicate with the brain and nervous system by different ways.

Microbes have the ability to produce neurochemicals or neurotransmitters that are exact analoges in structure to those produced by the host nervous system and act as vehicles for neurotransmitters and influence the mood and behavior [29]. Microbes have also shown immunomodulatory effect by the release of host immune factors such as cytokines and inflammatory mediators that have known neuronal targets within both the CNS & ENS [30]. Most of the lactic acid bacteria and Probiotics may also activate the vagal nerves, which interacts with all neurons involved in the alleviation of behavioural changes like anxiety, learning and memory, Depression etc. [28]. It has been demonstrated that a probiotic bacterium (L. rhamnosus JB-1) influences the emotional behaviour in mice mediated via GABA receptor [31].

Hence by above studies, it is observed that probiotics especially LAB could be useful in preventing/treating D-Galactose Induced Alzheimer's Disease. However, further research is required on higher mammalian experimental models such as rabbits, owl monkeys, vervet monkeys, squirrel monkeys, and so on to better understand the possible role of Lactobacillus strains in the protection against neurodegenerative diseases.

Conclusion

Antioxidant and ACh producing L. plantarum MTCC 1325 has Anti-Alzheimer properties against D-Galactose induced Alzheimer's disease since it resulted in body weight gain and organ index, improved the behavioral activity and learning skills through an elevation in the cholinergic neurotransmitter in the hippocampus and cerebral cortex regions of the brain and restored histopathological abnormalities back to the normal conditions.All these preliminary findings suggested that, the L. plantarum MTCC 1325 might have exerted

ameliorative effect against Alzheimer's disease induced by D-Galactose.

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Date of Submission: 30/01/2017 | **Date of Peer review**: 13/02/2017 | **Date of Acceptance**: 26/02/2017 | **Date of Publishing**: 04/03/2017

Financial or Other Competing Interests: None

How to cite this article
Mehta, V., Bhatt, K., Desai, N,. & Naik, M. (2017). Probiotics: An Adjuvant therapy for D-Galactose induced Alzheimer's disease. *Journal Of Medical Research And Innovation*, 1(1), 30-33.